



#23

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of
KAWADA, Kenji et al.
Serial No.: 09/214,277
Filed: March 1, 1999
NOVEL PARA-TERPHENYL COMPOUNDS

DECLARATION UNDER 37C.F.R. 1.132

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Honorable Commissioner
of Patents and Trademarks
Washington, D. C. 20231

Sir:

I, Dr. Akinori Arimura, a citizen of Japan, born in 1963 being duly sworn, depose and say as follows:

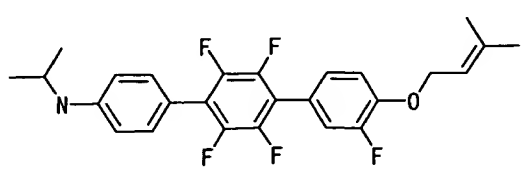
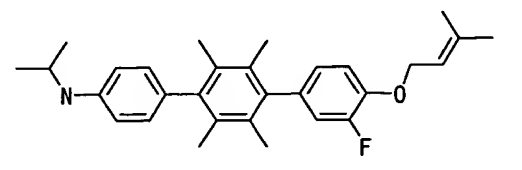
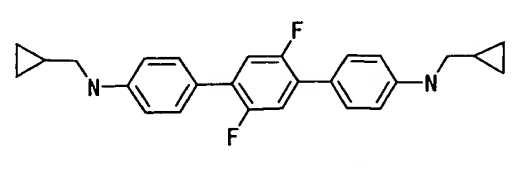
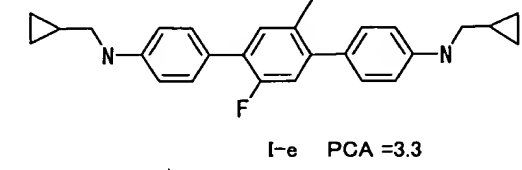
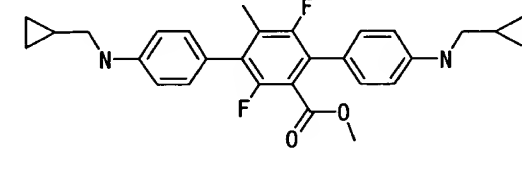
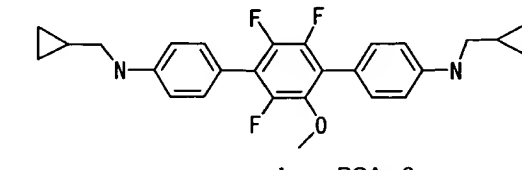
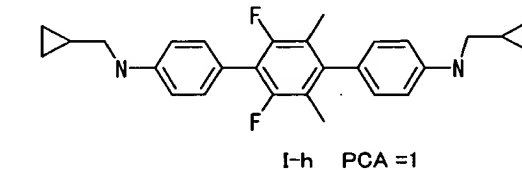
1. I graduated from Gifu Pharmaceutical University, Department of Pharmacy in March, 1986 and received the Ph. D degree of at Gifu Pharmaceutical University, in 1994.
2. Since April, 1988, I have been employed by Shionogi & Co., Ltd. and have been engaged in research work in the Drug Discovery Laboratories, SHIONOGI at 1-1, Futabacho 3-chome Toyonaka-shi, Osaka, Japan.
3. I am one of the inventors of the subject matter of United States Patent Application No. 09/214,277 filed on March 1, 1999 and I am intimately familiar with the contents of the application.

We measured the suppressive activity of the terphenyl compounds on the IgE production against ovalbumin (OVA) with the method described below and examined the affection of substituents in a terphenyl system.

EXPERIMENT

BALB/c mice were immunized by an intraperitoneal administration of 0.2 ml suspension of 2 µg of ovalbumin (OVA) and 2 mg of aluminium hydroxide gel in physiological saline. After test compounds were dissolved or suspended in N, N-dimethylacetamide, the mixture was diluted 20 times with miglyol 812 neutral oil. The obtained solution was orally administered to mice at 0.1 ml per mouse (dose 40 mg/kg). The administration was continued for 10 days from the immunizing day to the day before the blood collection. 10 days after the immunizing day, blood was collected from hearts, then sera were separated and stocked at -40 °C till the measurement of IgE antibody titer. The obtained mouse serum was 2-fold diluted with physiological saline, then each 50 µl of the solution was intradermally injected at dorsal skin of Wistar rats which previously hair cut. After 24 hours, a passive cutaneous anaphylaxis reaction (PCA) was induced by an intravenous injection of 0.5 ml of physiological saline containing 1 mg of OVA and 5 mg of Evans' blue dye. The rats were sacrificed 30 minutes later and the highest dilution giving bluing with a diameter of 5 mm or more was recorded as the PCA titer. For example, when a serum is positive for the PCA reaction till 2⁷ times dilution, the anti-OVA IgE antibody titer of the mouse is defined as 7.

RESULT

 <p>I-a PCA = 3.7</p>	 <p>I-b PCA = 0</p>
 <p>I-c PCA = 6.7</p>	 <p>I-e PCA = 3.3</p>  <p>I-f PCA = 4</p>  <p>I-g PCA = 0</p>  <p>I-h PCA = 1</p>

CONCLUSION

The compounds, listed in the left column, which were substituted only with halogen, had activity though it was weak. But the activity was remarkably raised by replacing fluorine to the substituents, such as methyl, methoxy, methoxycarbonyl group and so on, or by adding the substituents, such as methyl, methoxy, methoxycarbonyl group and so on, except for halogen. Such effect couldn't be expected at all.

I hereby declare that all statements made herein of my own knowledge are true and that statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date Sep 1, 2003

By Akinori Arimura